Barb only please

Access DB# 70558

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Dwayne C. Jones Examiner #: Dinsay Date: 09/30/02
Art Unit: 1619 Phone Number 30 8-4634 Serial Number: 09/529,459
Mail Box and Bldg/Room Location: 2007, CM1 Results Format Preferred (circle): PAPER DISK E-MAIL
2001, CM1

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Inhibition of PKC to treat Permeability Failure

Inventors (please provide full names): George Liang King, Dorr, MI

Earliest Priority Filing Date: 12 MAR 1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claims 16-19, 1P, 20 and 29

Point of Contact:
Barb O'Bryen
Technical Information Specialist
STIC CM1 6A05 308-4291

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: [illegible]	NA Sequence (#)	STN e-41
Searcher Phone #:	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up:	Bibliographic ✓	Dr.Link
Date Completed: 2-13-03	Litigation	Lexis/Nexis
Searcher Prep & Review Time: 20	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time: 6.4	Other	Other (specify) Chem Draw

PTO-1590 (8-01)

12. The method of claim 1, wherein said subject has already developed permeability disjunction.

13. The method of claim 1, wherein said subject has not yet developed permeability disjunction.

14. The method of claim 1, wherein said subject is at risk for renal failure.

15. The method of claim 14, wherein said subject is in end-stage renal failure.

16. A peritoneal dialysis fluid comprising a specific inhibitor of a PKC.

18. The dialysis fluid of claim 16, wherein said specific inhibitor is an inhibitor of PKC β.

19. The dialysis fluid of claim 18, wherein said inhibitor is a bis (indolyl) maleimide.

20. The dialysis fluid of claim 19, wherein said inhibitor is LY333531.

21. The dialysis fluid of claim 20, wherein said LY333531 is present in said dialysis fluid at about 1-1,000 nM.

22. The dialysis fluid of claim 16, wherein said dialysis fluid has a concentration of glucose of about 200nM.

23. A method of making an improved peritoneal dialysis fluid, comprising: providing a peritoneal dialysis fluid; and adding to that fluid a specific inhibitor of a PKC, to thereby provide an improved dialysis fluid.

24. A method of making an improved peritoneal dialysis fluid, comprising: providing a peritoneal dialysis fluid and adding LY333531 to the dialysis fluid.

AF/1600

Attorney's Docket No.: 10276-026001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : George Liang King
Serial No. : 09/524,459
Filed : March 10, 2000
Title : INHIBITION OF PKC TO TREAT PERMABILITY FAILURE

Art Unit : 1614
Examiner : D. Jones

BOX AF
Commissioner for Patents
Washington, D.C. 20231

AMENDMENT AND RESPONSE

In response to the final action mailed July 23, 2001, please amend the application as follows and consider the following remarks.

In the Claims:

Amend claim 24 as follows.

--24. (Amended) A method of making an improved peritoneal dialysis fluid, comprising: providing a peritoneal dialysis fluid and adding LY333531 to the dialysis fluid.--

Add new claims 25 to 29.

--25. A method of treating a subject, comprising: introducing into said subject a peritoneal dialysis fluid which includes an inhibitor of PKC β, an inhibitor of PKC γ, or an inhibitor of PKC δ, thereby treating said subject.

26. A method of treating a subject, comprising: introducing into said subject a peritoneal dialysis fluid which includes an inhibitor of PKC β.

27. A peritoneal dialysis fluid comprising an inhibitor of PKC β, an inhibitor of PKC γ, or an inhibitor of PKC δ.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

October 23, 2001
Date of Deposit

Signature

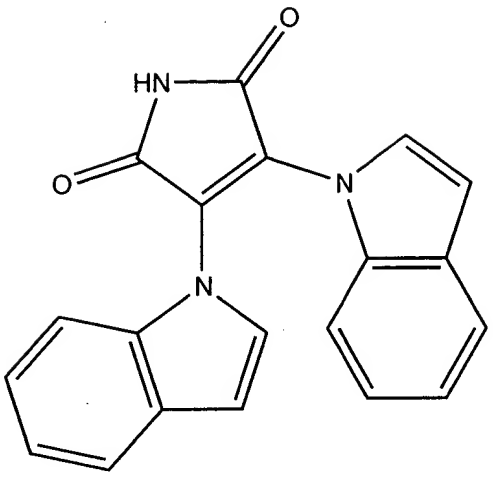
Typed or Printed Name of Person Signing Certificate

01/14/2002 CNGUYEN 00000152 09524459
01 FC:203 27.00 OP

01/16/2002 FPATTERS 00000002 061050 09524459
01 FC:202 168.00 CH

28. A peritoneal dialysis fluid comprising an inhibitor of PKC β.

29. A peritoneal dialysis fluid comprising LY333531.--



bis(indolyl)maleimide

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DICTIONARY FILE UPDATES:  17 JUL 2002  HIGHEST RN 439210-99-8

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide

L9   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   169939-94-0  REGISTRY
CN   9H,18H-5,21:12,17-Dimethenodibenzo[e,k]pyrrolo[3,4-
     h][1,4,13]oxadiazacyclohexadecine-18,20(19H)-dione, 9-
     [(dimethylamino)methyl]-6,7,10,11-tetrahydro-, (9S)- (9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   9H,18H-5,21:12,17-Dimethenodibenzo[e,k]pyrrolo[3,4-
     h][1,4,13]oxadiazacyclohexadecine-18,20(19H)-dione, 9-
     [(dimethylamino)methyl]-6,7,10,11-tetrahydro-, (S)-
OTHER NAMES:
CN   LY 333531
CN   Ruboxistaurin
FS   STEREOSEARCH
MF   C28 H28 N4 O3
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS,
       CASREACT, CHEMCATS, CIN, DRUGNL, DRUGUPDATES, EMBASE, PHAR, PROMT,
       SYNTHLINE, TOXCENTER, USPATFULL

Absolute stereochemistry.
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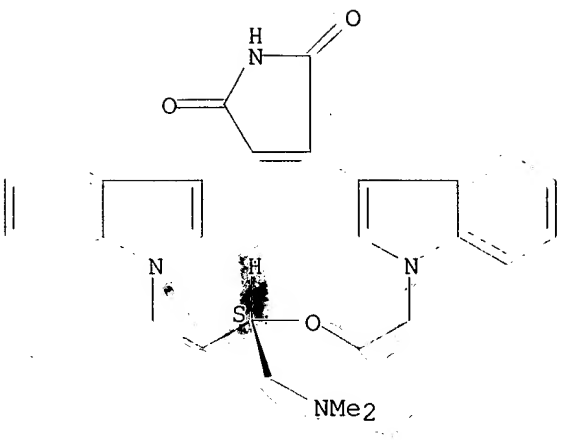

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

44 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
44 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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=> d que l83

L9            1 SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L17          76 SEA FILE=REGISTRY ABB=ON  2 333.151.57/RID AND 16.136.9/RID
L70         169 SEA RUBOXISTAURIN OR LY333531 OR LY 333531 OR L9
L71        2072 SEA (BISINDOLYL OR BIS(L) INDOLYL)(L) MALEIMIDE# OR BISINDOLYLM
                ALEIMIDE# OR L17
L72       50344 SEA (PROTEIN KINASE C OR PKC)(5A)(ANTAG? OR INHIBIT?)
L73      136872 SEA DIALY? OR HEMODIALY? OR HAEMODIALY?
L76       13929 SEA DIALY!ATE# OR DIALYSIS(2A)(SOLUTION# OR FLUID#)
L77      154829 SEA ?PERITONE?
L80      178121 SEA (RENAL OR KIDNEY#)(5A)(DISEASE# OR FAILURE# OR DYSFUNCTION?
                )
L83          18 SEA ((L70 OR L71 OR L72)) AND ((L77(15A) L73) OR L80) AND L76


=> fil capl; d que l24; d que l22; d que l26; d que l27
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FILE COVERS 1907 - 18 Jul 2002 VOL 137 ISS 3
FILE LAST UPDATED: 17 Jul 2002 (20020717/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

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L9            1 SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L10          85 SEA FILE=CAPLUS ABB=ON  L9 OR RUBOXISTAURIN OR LY333531 OR LY
                333531
L17          76 SEA FILE=REGISTRY ABB=ON  2 333.151.57/RID AND 16.136.9/RID
L18         129 SEA FILE=CAPLUS ABB=ON  L17 OR (BISINDOLYL OR BIS(L)INDOLYL)(L)
                MALEIMIDE#/OBI OR BISINDOLYLMALEIMIDE#/OBI
L19       48954 SEA FILE=CAPLUS ABB=ON  (DIALYSIS OR DIALY!ATE#)
L24           1 SEA FILE=CAPLUS ABB=ON  (L18 OR L10) AND L19
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= bis indolyl maleimides

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L5            1 SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C"/CN
L6        20456 SEA FILE=CAPLUS ABB=ON  L5
L7        28310 SEA FILE=CAPLUS ABB=ON  (PKC OR PROTEIN KINASE C)/OBI
L8         4761 SEA FILE=CAPLUS ABB=ON  (L6 OR L7)(L)(INHIBIT? OR ANTAG?)
L19       48954 SEA FILE=CAPLUS ABB=ON  (DIALYSIS OR DIALY!ATE#)
L20       42166 SEA FILE=CAPLUS ABB=ON  ?PERITONEAL?
L21        2415 SEA FILE=CAPLUS ABB=ON  L19(L)L20
L22           1 SEA FILE=CAPLUS ABB=ON  L8 AND L21
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L5            1 SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C"/CN
L6        20456 SEA FILE=CAPLUS ABB=ON  L5
L7        28310 SEA FILE=CAPLUS ABB=ON  (PKC OR PROTEIN KINASE C)/OBI
L8         4761 SEA FILE=CAPLUS ABB=ON  (L6 OR L7)(L)(INHIBIT? OR ANTAG?)
L25       10648 SEA FILE=CAPLUS ABB=ON  DIALYSIS/CT OR DIALYSIS FLUIDS/CT
L26           1 SEA FILE=CAPLUS ABB=ON  L25 AND L8
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L5            1 SEA FILE=REGISTRY ABB=ON  "PROTEIN KINASE C"/CN
L6        20456 SEA FILE=CAPLUS ABB=ON  L5
L7        28310 SEA FILE=CAPLUS ABB=ON  (PKC OR PROTEIN KINASE C)/OBI
L8         4761 SEA FILE=CAPLUS ABB=ON  (L6 OR L7)(L)(INHIBIT? OR ANTAG?)
L19       48954 SEA FILE=CAPLUS ABB=ON  (DIALYSIS OR DIALY!ATE#)
L27           1 SEA FILE=CAPLUS ABB=ON  L19(L)L8
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=> s l24 or l22 or l26 or l27

L84           1 L24 OR L22 OR L26 OR L27

=> fil wpids

FILE 'WPIDS' ENTERED AT 10:02:18 ON 18 JUL 2002
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FILE LAST UPDATED: 17 JUL 2002              <20020717/UP>
MOST RECENT DERWENT UPDATE            200245   <200245/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE
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>>> The BATCH option for structure searches has been
    enabled in WPINDEX/WPIDS and WPIX  >>>

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

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    GUIDES, PLEASE VISIT:
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=> d que l34

L29       10802 SEA FILE=WPIDS ABB=ON  DIALY?
L30         571 SEA FILE=WPIDS ABB=ON  PROTEIN KINASE C OR PKC
L31         323 SEA FILE=WPIDS ABB=ON  L30(5A)(INHIBIT? OR ANTAG?)
L32           3 SEA FILE=WPIDS ABB=ON  RUBOXISTAURIN OR LY333531 OR LY 333531
L33          24 SEA FILE=WPIDS ABB=ON  (BISINDOLYL OR BIS(L)INDOLYL)(L)MALEIMID
                E# OR BISINDOLYLMALEIMIDE#
L34           4 SEA FILE=WPIDS ABB=ON  L29 AND (L31 OR L32 OR L33)


=> fil biosis; d que l43

FILE 'BIOSIS' ENTERED AT 10:02:20 ON 18 JUL 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
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RECORDS LAST ADDED: 17 July 2002 (20020717/ED)



L9            1 SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L17          76 SEA FILE=REGISTRY ABB=ON  2 333.151.57/RID AND 16.136.9/RID
L35          78 SEA FILE=BIOSIS ABB=ON  RUBOXISTAURIN OR LY333531 OR LY 333531
                OR L9
L36         900 SEA FILE=BIOSIS ABB=ON  (BISINDOLYL OR BIS(L)INDOLYL)(L)MALEIMI
                DE# OR BISINDOLYLMALEIMIDE# OR L17
L37       14270 SEA FILE=BIOSIS ABB=ON  (PROTEIN KINASE C OR PKC)(5A)(ANTAG?
                OR INHIBIT?)
L38       61639 SEA FILE=BIOSIS ABB=ON  DIALY?
L39          98 SEA FILE=BIOSIS ABB=ON  (L35 OR L36 OR L37) AND L38
L41       91916 SEA FILE=BIOSIS ABB=ON  ?PERITONEAL?
L42       94818 SEA FILE=BIOSIS ABB=ON  (RENAL OR KIDNEY#)(5A)(DISEASE# OR
                FAILURE# OR DYSFUNCTION?)
L43           8 SEA FILE=BIOSIS ABB=ON  L39 AND (L41 OR L42)


=> fil medl; d que l50

FILE 'MEDLINE' ENTERED AT 10:02:21 ON 18 JUL 2002

 FILE LAST UPDATED: 17 JUL 2002 (20020717/UP).  FILE COVERS 1958 TO DATE.
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On June 9, 2002, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

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L9            1 SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L17          76 SEA FILE=REGISTRY ABB=ON  2 333.151.57/RID AND 16.136.9/RID
L45        2502 SEA FILE=MEDLINE ABB=ON  DIALYSIS SOLUTIONS+NT/CT
L46       54625 SEA FILE=MEDLINE ABB=ON  RENAL DIALYSIS+NT/CT
L47        6704 SEA FILE=MEDLINE ABB=ON  PROTEIN KINASE C/CT(L)AI/CT
L48          46 SEA FILE=MEDLINE ABB=ON  RUBOXISTAURIN OR LY333531 OR LY
                333531 OR L9
L49         805 SEA FILE=MEDLINE ABB=ON  (BISINDOLYL OR BIS(L)INDOLYL)(L)MALEIM
                IDE# OR BISINDOLYLMALEIMIDE# OR L17
L50           1 SEA FILE=MEDLINE ABB=ON  (L45 OR L46) AND (L47 OR L48 OR L49)
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=> fil embase

FILE 'EMBASE' ENTERED AT 10:02:22 ON 18 JUL 2002

FILE COVERS 1974 TO 11 Jul 2002 (20020711/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

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=> d que l68;d que l69

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L9            1 SEA FILE=REGISTRY ABB=ON  "LY 333531"/CN
L17          76 SEA FILE=REGISTRY ABB=ON  2 333.151.57/RID AND 16.136.9/RID
L51        1659 SEA FILE=EMBASE ABB=ON  DIALYSIS FLUID/CT
L53       41996 SEA FILE=EMBASE ABB=ON  HEMODIALYSIS+NT/CT
L54          76 SEA FILE=EMBASE ABB=ON  RUBOXISTAURIN OR LY333531 OR LY 333531
                OR L9
L55         853 SEA FILE=EMBASE ABB=ON  (BISINDOLYL OR BIS(L)INDOLYL)(L)MALEIMI
                DE# OR BISINDOLYLMALEIMIDE# OR L17
L58           2 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C ALPHA INHIBITOR/CT
L60           4 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C BETA INHIBITOR/CT
L62        3014 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C INHIBITOR/CT
L67         690 SEA FILE=EMBASE ABB=ON  PERITONEAL DIALYSIS FLUID/CT
L68           0 SEA FILE=EMBASE ABB=ON  (L51 OR L53 OR L67) AND (L54 OR L55 OR
                L58 OR L60 OR L62)



L51        1659 SEA FILE=EMBASE ABB=ON  DIALYSIS FLUID/CT
L53       41996 SEA FILE=EMBASE ABB=ON  HEMODIALYSIS+NT/CT
L56       23177 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C/CT
L57         124 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C ALPHA/CT
L59          51 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C BETA/CT
L61          24 SEA FILE=EMBASE ABB=ON  PROTEIN KINASE C GAMMA/CT
L63       67124 SEA FILE=EMBASE ABB=ON  ENZYME INHIBITOR/CT OR ENZYME INHIBITIO
                N/CT
L67         690 SEA FILE=EMBASE ABB=ON  PERITONEAL DIALYSIS FLUID/CT
L69           0 SEA FILE=EMBASE ABB=ON  (L51 OR L53 OR L67) AND (L56 OR L57 OR
                L59 OR L61) AND L63
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=> dup rem l50,l83,l84,l43,l34
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PROCESSING COMPLETED FOR L84
PROCESSING COMPLETED FOR L43
PROCESSING COMPLETED FOR L34
L85          18 DUP REM L50 L83 L84 L43 L34 (14 DUPLICATES REMOVED)
                ANSWER '1' FROM FILE MEDLINE
                ANSWERS '2-6' FROM FILE DRUGU
                ANSWERS '7-8' FROM FILE BIOTECHNO
                ANSWERS '9-10' FROM FILE ESBIOBASE
                ANSWERS '11-13' FROM FILE SCISEARCH
                ANSWER '14' FROM FILE CAPLUS
                ANSWER '15' FROM FILE BIOSIS
                ANSWERS '16-18' FROM FILE WPIDS

=> d ibib ab hitrn 1-18; fil hom

L85  ANSWER 1 OF 18     MEDLINE                          DUPLICATE 5
ACCESSION NUMBER:   2001467746     MEDLINE
DOCUMENT NUMBER:    21403571   PubMed ID: 11512674
TITLE:              Hyaluronan fragments induce the synthesis of MCP-1 and IL-8
                    in cultured human peritoneal mesothelial cells.
AUTHOR:             Haslinger B; Mandl-Weber S; Sellmayer A; Sitter T
CORPORATE SOURCE:   Medizinische Klinik Innenstadt, Klinikum der
                    Ludwig-Maximilians Universitat, Munich, Germany.
SOURCE:             CELL AND TISSUE RESEARCH, (2001 Jul) 305 (1) 79-86.
                    Journal code: 0417625. ISSN: 0302-766X.
PUB. COUNTRY:       Germany: Germany, Federal Republic of
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200201
ENTRY DATE:         Entered STN: 20010830
                    Last Updated on STN: 20020130
                    Entered Medline: 20020129
AB   Human peritoneal mesothelial cells (HMC) play an important role in
```

inflammatory processes by their ability to produce various cytokines and chemokines, such as monocyte chemoattractant protein 1 (MCP-1) and interleukin 8 (IL-8). In this study we investigated the effect of experimentally generated hyaluronan (HA) fragments, degradation products of the extracellular matrix component hyaluronan, which accumulate at inflammatory sites, on the expression of MCP-1 and IL-8 in cultured HMC. MCP-1 and IL-8 mRNA expression was determined by RNase protection assays, and protein levels in the supernatants were measured by enzyme-linked immunosorbent assays. HA fragments with a molecular mass of approximately 1-7x10(5) daltons upregulate MCP-1 and IL-8 synthesis in HMC dose and time dependently. The effect of HA fragments could be blocked by Ro31-8220, a specific protein kinase C inhibitor, and by PD98059, an inhibitor of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway. Upregulation of chemokine synthesis was preceded by an increase in NF-kappaB and AP-1 DNA-binding activity, suggesting that these transcription factors are activated to increase MCP-1 and IL-8 expression by HA fragments. These data demonstrate that HA fragments markedly enhance the mRNA expression and protein synthesis of MCP-1 and IL-8 in HMC. In concert with previous findings, our observations indicate that enhanced levels of HA, which are present in the peritoneal cavity of peritoneal dialysis patients, may account for a locally increased chemokine production.

L85 ANSWER 2 OF 18 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1998-40207 DRUGU T S
TITLE: Pseudoporphyria cutanea tarda induced by furosemide in a patient undergoing **peritoneal dialysis**.
AUTHOR: Breier F; Feldmann R; Pelzl M; Gschnait F
LOCATION: Vienna, Austria
SOURCE: Dermatology (197, No. 3, 271-73, (1998) 3 Fig. 22 Ref.
CODEN: DERAEG ISSN: 1018-8665
AVAIL. OF DOC.: Department of Dermatology, Lainz Municipal Hospital, Wolkersbergenstrasse 1, A-1130 Vienna, Austria. (e-mail: brf@khl.magwien.ac.at).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB A case of pseudoporphyria cutanea tarda (PP) induced by furosemide is reported in a patient who was undergoing **peritoneal dialysis** for diabetic nephropathy. Histopathology of an early lesion revealed a subepidermal cleft under a normal epidermis with single necrotic keratinocytes and normal dermal structures. A subepidermal bulla and caterpillar bodies (CB) were discovered in the epidermis in an advanced lesion. Uroporphyrin and coproporphyrin levels of serum, urine and **dialysate** were found to be normal repeatedly, leading to the diagnosis of PP. The patient's medication included furosemide, prazosin hydrochloride, nitrendipine, calcium dobesilate, ferrosulfate, ranitidine, cisapride, insulin and erythropoietin. Furosemide was switched with ethacrynic acid and the blisters spontaneously resolved. At the 1-yr follow up, the patient remained free of lesions.

L85 ANSWER 3 OF 18 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-40926 DRUGU P S
TITLE: Effects of intraperitoneal chemotherapy on peritoneal adhesions: experimental studies.
AUTHOR: Demez P; Jacquet P; Chang D; Sugarbaker P H; Jacquet N
LOCATION: Liege, Belg.; Washington, D.C., USA
SOURCE: ; Proc.Am.Soc.Clin.Oncol. (15, 32 Meet., 224, 1996).
CODEN: ; 7790
AVAIL. OF DOC.: CHU Liege, Belgium.
LANGUAGE: English
DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB A rat model of peritoneal adhesion was designed in order to test the effect and the timing of administration of different i.p. drugs (mitomycin C (MMC), 5-fluorouracil (5-FU), doxorubicin (DOX), cisplatin (CDDP), and mitoxantrone (MIT)) on post-operative adhesions. Animals treated at the end of surgery by MMC, 5-FU, or DOX showed a lower adhesion score vs. rats treated by **peritoneal dialysis solution** (PDS) alone. There was no difference of adhesion score between animals treated by CDDP and control group. Animals treated by MIT showed a higher adhesion score compared to control group. When administered 48 hr after the surgery, none of the CT regimens changed the adhesion score. These data suggest that intra-operative MMC, 5-FU, or CDDP may decrease the incidence of post-operative adhesion. Intra-operative administration of MIT may worsen the rate of adhesion. (conference abstract).

L85 ANSWER 4 OF 18 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1995-32649 DRUGU P B E
TITLE: A sensitive (Na,K)ATPase assay specific for inhibitors acting through the digitalis-binding site.
AUTHOR: Tao Q F; Soszynski P A; Hollenberg N K; Graves S W
LOCATION: Boston, Mass., USA
SOURCE: J.Cardiovasc.Pharmacol. (25, No. 6, 859-63, 1995) 3 Fig. 21 Ref.
CODEN: JCPCDT ISSN: 0160-2446
AVAIL. OF DOC.: Endocrine-Hypertension Division, Brigham and Women's Hospital, 221 Longwood Ave., Boston, MA 02115, U.S.A. (S.W.G.).
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB Ouabain, digoxin and bufalin (all Sigma-Chem.) showed greater inhibition of calf kidney (Na,K)ATPase in a sensitive assay (SA) that included a pre-incubation step than in the conventional assay (CA). Similarly, enhanced inhibition in the SA was observed for endogenous Na pump inhibitor (ESPI) from **peritoneal dialysate** of volume-expanded **renal failure** patients, for 17-OH-progesterone (17-OH-P) and for dehydroepiandrosterone (DHEA, prasterone, both Sigma-Chem.). There was no such enhancement in the SA compared with CA for oleic acid, lysophosphatidyl choline (LPC, lysolecithin), vanadate, tamoxifen or AgNO3 (all Sigma-Chem.). Use of SA and CA together may be useful in evaluating Na pump inhibitors that interact with the digitalis receptor.

L85 ANSWER 5 OF 18 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1995-45581 DRUGU P
TITLE: Furosemide disposition in patients on CAPD.
AUTHOR: Martin U; Winney R J; Prescott L F
LOCATION: Edinburgh, U.K.
SOURCE: Eur.J.Clin.Pharmacol. (48, No. 5, 385-90, 1995) 3 Fig. 2 Tab. 28 Ref.
CODEN: EJCPAS ISSN: 0031-6970
AVAIL. OF DOC.: Clinical Pharmacology Unit, The Royal Infirmary, Edinburgh EH3 9YW, Scotland.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB P.o. and i.v. furosemide (Lasix, Hoechst) disposition differed in 11 patients with **renal failure** on continuous ambulatory **peritoneal dialysis** (CAPD) and 8 healthy subjects.

Concomitant therapy was iron, folate and aluminum hydroxide, and also prednisolone, ranitidine, metoprolol, alfacalcidol, thyroxine, isosorbide mononitrate, nifedipine, aspirin, digoxin, gliclazide, diltiazem and captopril for asthma, angina pectoris, hypertension, celiac disease, hypothyroidism and pernicious anemia. Furosemide absorption was not significantly different between the 2 groups. Elimination half-life was longer in the CAPD patients. Renal clearance was much lower in the CAPD patients. It is concluded that the differences in furosemide disposition in CAPD patients are due to **renal failure**.

L85 ANSWER 6 OF 18 DRUGU COPYRIGHT 2002 THOMSON DERWENT
ACCESSION NUMBER: 1993-47965 DRUGU T S
TITLE: Fetal Exposure to Lisinopril: Neonatal Manifestations and Management.
AUTHOR: Bhatt Mehta V; Deluga K S
LOCATION: Ann Arbor, Michigan, United States
SOURCE: Pharmacotherapy (13, No. 5, 515-18, 1993) 1 Tab. 21 Ref.
CODEN: PHPYDQ ISSN: 0277-0008
AVAIL. OF DOC.: Department of Pharmacy, F-5203 C.S. Mott Children's Hospital, 200 East Hospital Drive, Ann Arbor, MI 48109-0225, U.S.A.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AB The case of a premature infant with chronic **renal failure** who was exposed to lisinopril (Zestril, LIS) in utero throughout pregnancy is reported. LI was administered to treat maternal hypertension. Serum LI levels and suppressed ACE activity during anuria indicated that the drug had a prolonged half-life. Furosemide did not counter anuria during the 1st 8 wk. Dopamine was started for hypotension. **Peritoneal dialysis** reduced serum LI and normalized PRA and ACE activity. The infant became very hypertensive and his response to hydralazine and propranolol was minimal and nitroprusside sodium was used. Hypertension responded to i.v. enalapril (EN). Adequate renal function did not return and extensive atrophy, loss of renal tubules and interstitial fibrosis were observed at open renal biopsy.

L85 ANSWER 7 OF 18 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.DUPLICATE
ACCESSION NUMBER: 2001:34205799 BIOTECHNO
TITLE: Hexamethylene bisacetamide protects peritoneal mesothelial cells from glucose
AUTHOR: Ogawa T.; Hayashi T.; Yorioka N.; Kyoizumi S.; Trosko J.E.
CORPORATE SOURCE: Dr. T. Ogawa, Nephrology Division, Hiroshima Prefectural Hospital, 1-5-54, Ujina-Kanda, Minami-ward, Hiroshima 734-8530, Japan.
E-mail: tk-ogawa@msh.biglobe.ne.jp
SOURCE: Kidney International, (2001), 60/3 (996-1008), 53 reference(s)
CODEN: KDYIA5 ISSN: 0085-2538
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background. **Peritoneal dialysis** causes damage to **peritoneal** mesothelial cells primarily because **dialysis fluids** have a high glucose concentration. This study examined the abnormalities of gap junctional intercellular communication (GJIC) in human peritoneal mesothelial cells (HPMCs) exposed to relatively high levels of glucose. Also, ability of hexamethylene bisacetamide (HMBA) to up-regulate GJIC in HPMCs exposed to high levels of glucose was measured. Methods. An assay that monitors the recovery of fluorescence after

photobleaching was used to measure GJIC in primary cultured HPMCs. The cells were exposed to a low (10 mmol/L) or high (50 or 90 mmol/L) glucose level for a total of six days, and some cells were also incubated with or without HMBA (1 or 6 mmol/L) from day 4. The effects of incubation in these various environments on expression of the connexin 43 (Cx43) gene were investigated by the reverse transcription-polymerase chain reaction (to detect Cx43 mRNA) or by immunofluorescence and Western blotting (to detect Cx43 protein). To evaluate the influence of protein kinase C (PKC) or mitogen-activated protein kinase (MAPK) on GJIC, specific inhibitors were added to cultures in a high glucose medium. Results. Gap junctional intercellular communication was inhibited in a concentration- and time-dependent manner when cells were exposed to high glucose. The addition of 6 mmol/L HMBA to cultures significantly enhanced GJIC despite the presence of a high glucose concentration. High glucose also down-regulated Cx43 mRNA and protein expression, with the dose-dependent decrease of Cx43 protein at gap junctions paralleled by a decrease in the phosphorylation of this protein. As expected, treatment of cells with 6 mmol/L HMBA increased both Cx43 mRNA and protein levels despite exposure to high glucose. The addition of **PKC** or MAPK **inhibitors** to high glucose cultures did not restore GJIC, and there was no significant change of Cx43 phosphorylation in the presence of these inhibitors. Conclusions. High glucose down-regulates GJIC in human peritoneal mesothelial cells. It also decreases the levels of both Cx43 mRNA and Cx43 protein, with the latter becoming hypophosphorylated. HMBA appears to reverse all of these changes. These results are consistent with our hypothesis that HMBA protects HPMCs from the adverse effects of high glucose by reversing various processes that would otherwise lead to harmful loss of GJIC.

L85 ANSWER 8 OF 18 BIOTECHNO COPYRIGHT 2002 Elsevier Science B.V.DUPLICATE

ACCESSION NUMBER: 2001:32260836 BIOTECHNO

TITLE: Effect of high glucose concentration on the synthesis of monocyte chemoattractant protein-1 in human peritoneal mesothelial cells: Involvement of protein kinase C

AUTHOR: Haslinger B.; Mandl-Weber S.; Sellmayer A.; Lederer S.R.; Sitter T.

CORPORATE SOURCE: Dr. T. Sitter, Medizinische Klinik, Klin. Innenstadt der Univ. Munchen, Ziemssenstrasse 1, D-80336 Munchen, Germany.
E-mail: tsitter@medinn.med.uni-muenchen.de

SOURCE: Nephron, (2001), 87/4 (346-351), 24 reference(s)
CODEN: NPRNAY ISSN: 0028-2766

DOCUMENT TYPE: Journal; Article

COUNTRY: Switzerland

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Human peritoneal mesothelial cells (HMC) contribute to the activation and control of inflammatory processes in the peritoneum by their potential to produce various inflammatory mediators. The present study was designed to assess the effect of glucose, the osmotic active compound in most commercially available **peritoneal dialysis fluids**, on the synthesis of the C-C chemokine monocyte chemoattractant protein-1 (MCP-1) in cultured HMC. The MCP-1 concentration in the cell supernatants was determined by enzyme-linked immunosorbent assay and the MCP-1 mRNA expression was examined using Northern blot analysis. Incubation of HMC with glucose (30-120 mM) resulted in a time- and concentration-dependent increase in MCP-1 protein secretion and mRNA expression. After 24 h the MCP-1 synthesis was increased from 2.8 .+-. 0.46 to 4.2 .+-. 0.32 ng/10.sup.5 cells (n = 5, p < 0.05) in HMC treated with 60 mM glucose. In contrast, osmotic control media containing either the metabolically inert monosaccharide mannitol or NaCl did not influence MCP-1 production. The stimulating effect of

high glucose on MCP-1 expression in HMC was mimicked by activation of protein kinase C (PKC) with the phorbol ester PMA (20 nM). Coincubation of the cells with glucose and the specific **PKC inhibitor** Ro 31-8220 completely blunted glucose-mediated MCP-1 expression. In summary, our results indicate that glucose induces MCP-1 synthesis by a PKC-dependent pathway. Since osmotic control media did not increase MCP-1 release, it is suggested that the effect of glucose is mainly related to metabolism and not to hyperosmolarity. These data may in part explain elevated steady-state levels of MCP-1 found in the **dialysis** effluent of continuous ambulatory **peritoneal dialysis** patients. Copyright .COPYRGT. 2001 S. Karger AG, Basel.

L85 ANSWER 9 OF 18 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V.
DUPLICATE

ACCESSION NUMBER: 2001046352 Elsevier BIOBASE
TITLE: High glucose-induced PKC activation mediates TGF-.beta.1 and fibronectin synthesis by peritoneal mesothelial cells
AUTHOR: Ha H.; Mi Ra Yu; Hi Bahl Lee
CORPORATE SOURCE: Dr. H.B. Lee, Hyonam Kidney Laboratory, Soon Chun Hyang University, 657 Hannam Dong, Yongsan Ku, Seoul 140-743, South Korea.
E-mail: hblee@seoul.com
SOURCE: Kidney International, (2001), 59/2 (463-470), 34 reference(s)
CODEN: KDYIA5 ISSN: 0085-2538
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Background. Progressive **peritoneal** fibrosis, membrane hyperpermeability, and ultrafiltration failure have been observed in long-term **peritoneal dialysis** (PD) using glucose as an osmotic agent. High glucose activates protein kinase C (PKC), which is one important signal pathway in the activation of transforming growth factor-.beta.1 (TGF-.beta.1) and fibronectin (FN). To gain a better understanding of mechanisms involved in peritoneal fibrosis, we examined the effects of high glucose on human peritoneal mesothelial cell (HPMC) TGF-.beta.1 and FN mRNA expression and protein synthesis and determined the involvement of PKC in the high glucose-induced HPMC activation. Methods. Synchronized confluent HPMC were incubated with different concentrations of glucose with and without **inhibition** of **PKC**. **PKC** activity and diacylglycerol (DAG) levels were measured. The expression of TGF-.beta.1 and FN mRNAs by HPMC was measured by Northern blot analysis. TGF-.beta.1 protein was measured by enzyme-linked immunosorbent assay (ELISA) and mink lung epithelial cell growth inhibition assay. FN protein was measured by Western blot analysis and ELISA. Results. PKC activity and DAG levels in HPMC cultured under 50 mmol/L (high) glucose increased 2.3- and 2.0-fold, respectively, that of 5.6 mmol/L (control) glucose at 24 hours and this was sustained up to 72 hours. The expression of TGF-.beta.1 and FN mRNA by HPMC cultured under high glucose increased 1.6- and 1.7-fold, respectively, that of control values at 24 hours. TGF-.beta. bioaetivity as well as protein content in heat-activated conditioned media from high glucose was significantly higher than that of control values at 24 and 48 hours. FN protein also increased in response to high glucose, as measured by Western blot analysis and ELISA. PKC activator phorbol 12-myristate 13-acetate (PMA) induced 2.2- and 1.4-fold increase in TGF-.beta.1 and FN mRNA expression, respectively. Depletion of **PKC** and calphostin C, a **PKC inhibitor**, effectively prevented both PMA and high glucose-induced, but not constitutive, expression of TGF-.beta.1 and FN. Conclusion. The present data demonstrate that high glucose up-regulates TGF-.beta.1 and FN synthesis by HPMC, and that this high glucose-induced

up-regulation is largely mediated by PKC. These results suggest that activation of PKC by high glucose in conventional PD solutions may constitute an important signal for activation of HPMC, leading to progressive accumulation of extracellular matrix and eventual peritoneal fibrosis.

L85 ANSWER 10 OF 18 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V. DUPLICATE

ACCESSION NUMBER: 1996148432 Elsevier BIOBASE
TITLE: Intraperitoneal coagulation and fibrinolysis during inflammation: In vivo and in vitro observations
AUTHOR: Sitter T.; Godde M.; Spannagl M.; Fricke H.; Kooistra T.
CORPORATE SOURCE: Dr. T. Sitter, Medizinische Klinik, Klinikum Innenstadt, Universitat Munchen, Ziemssenstr. 1, D-80336 Munchen, Germany.
SOURCE: Fibrinolysis, (1996), 10/SUPPL. 2 (99-104)
CODEN: FBRIE7 ISSN: 0268-9499
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United Kingdom
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We used continuous **peritoneal dialysis** (CAPD) as a model to study intraperitoneal fibrin turnover during peritonitis. Activation markers of coagulation and fibrinolysis including prothrombin fragment F1+2 (F1+2), thrombin antithrombin III complex (TAT), fibrin monomer (FM), and fibrin degradation products (FbDP) were measured in the **peritoneal dialysis** effluents from 23 CAPD patients. In the **dialysate** of patients who had not suffered from peritonitis during the last 6 months (n = 18) we found remarkably high levels of F1+2, TAT and FM concomitant with a high concentration of FbDP, indicating a high rate of intraperitoneal fibrin turnover. The balance between peritoneal generation and degradation of fibrin was disturbed in untreated patients with acute peritonitis (n = 5), who had significantly higher levels of coagulation markers and a higher ratio between FM and FbDP. To evaluate the role of mesothelial cells (MC) in the high peritoneal fibrin turnover, we investigated the expression of tissue-type plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA), plasminogen activator inhibitor type-1 (PAI-1) and tissue factor (TF) in cultured human peritoneal MC under basal conditions and after exposition to tumor necrosis factor .alpha. (TNF.alpha.), interleukin-1.alpha. (IL-1.alpha.) or bacterial lipopolysaccharide (LPS). The exposure of MC to TNF.alpha., or to a lesser extent, IL-1.alpha. or LPS, reduced their fibrinolytic activity by decreasing t-PA production and increasing PAI-1 synthesis. Furthermore the addition of TNF.alpha. resulted in an activation of the coagulation cascade by the expression of TF. We found that the isoflavone compound genistein (25 .mu.g/ml) prevented the TNF.alpha.-induced expression of PAI-1 and TF, while also slightly counteracting the decrease in t-PA synthesis. The **protein kinase C inhibitor**, Ro 31-8220 (3.mu.M), only moderately opposed the TNF.alpha.-induced changes in t-PA and PAI-1 synthesis, but completely prevented the induction of TF mRNA. In summary our in vitro findings explain the disbalance between intraperitoneal coagulation and fibrinolyis during peritonitis in vivo. To restore the balance between fibrinolysis and coagulation under inflammatory conditions attempts to interfere with the TNF.alpha. signalling pathway could be a new therapeutic approach.

L85 ANSWER 11 OF 18 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 3

ACCESSION NUMBER: 2001:370718 SCISEARCH
THE GENUINE ARTICLE: 428UF
TITLE: Advantages of pyruvate over lactate in **peritoneal dialysis solutions**

AUTHOR: [redacted] (Reprint)
CORPORATE SOURCE: Fresenius Neomed Dialysis Ctr Chicago, Chicago, IL 60008 USA (Reprint); Hines Loyola Med Ctr, Dept Med, Renal & Hypertens Sect, Hines, IL 60141 USA
COUNTRY OF AUTHOR: USA
SOURCE: ACTA PHARMACOLOGICA SINICA, (MAY 2001) Vol. 22, No. 5, pp. 385-392.
Publisher: ACTA PHARMACOLOGICA SINICA, 294 TAI-YUAN ROAD, SHANGHAI 200031, PEOPLES R CHINA.
ISSN: 0253-9756.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 36

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB This review discusses effects of both lactate and pyruvate, and high glucose in **peritoneal dialysis solutions** (PDS) on leukocytes, mainly on intracellular pH ([pH](i)), glucose metabolic pathways, and apoptosis. Lactate-based PDS (L-PDS) are bioincompatible primarily due to the low pH, high lactate, and glucose excess in both individual and combination. High lactate in an acidi milieu would induce severe intracellular acidosis of leukocytes, and high glucose may disturb glucose metabolic pathways and activate protein kinase C (PKC) and nuclear factor-kappa B (NF-kappa B) of the cells, leading to apoptosis. Pyruvate-based PDS (P-PDS) are novel experimental PDS. Evidence shows that P-PDS are superior in biocompatibility. Pyruvate protection of cells has been confirmed in many fields besides the PDS area. Although the underlying mechanism whereby P-PDS preserve cell function is not fully understood, it may be associated with the maintenance of [pH](i) close to physiological, due to its low buffering capacity, improvement of cellular glucose metabolic pathways and redox state, and sustainment of intracellular calcium ([Ca2+](i)) homeostasis in high glucose concentrations. It may also **inhibit PKC** and NF-kappa B activation in high glucose. In addition, pyruvate is a strong antioxidant, a scavenger of hydrogen peroxide (H2O2). However, exogenous pyruvate in PDS could not be an energy source for cells and also the Crabtree effect might not occur in neutrophils. Pyruvate is a hopeful candidate of buffers in PDS in the near future. Further observation of P-PDS is strongly needed with peritoneal cells to verify the cell protection both in vitro and in vivo before clinic trials.

L85 ANSWER 12 OF 18 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 7
ACCESSION NUMBER: 1999:694105 SCISEARCH
THE GENUINE ARTICLE: 233HH
TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human peritoneal mesothelial cells
AUTHOR: Sitter T (Reprint); MandlWeber S; Wornle M; Haslinger B; Goedde M; Kooistra T
CORPORATE SOURCE: UNIV MUNICH, KLINIKUM INNENSTADT, MED KLIN, ZIEMSSENSTR 1, D-80336 MUNICH, GERMANY (Reprint); TNO, PG, GAUBIUS LAB, LEIDEN, NETHERLANDS
COUNTRY OF AUTHOR: GERMANY; NETHERLANDS
SOURCE: THROMBOSIS AND HAEMOSTASIS, (SEP 1999) Vol. 82, No. 3, pp. 1171-1176.
Publisher: F K SCHATTAUER VERLAG GMBH, P O BOX 10 45 43, LENZHALDE 3, D-70040 STUTTGART, GERMANY.
ISSN: 0340-6245.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 31

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Physical and chemical irritation of the **peritoneum** through

glucose-based hyperosmolar **dialysis solutions** results in a nonbacterial serositis with fibrinous exudation. Thereby, human **peritoneal** mesothelial cells (HMC) play an important role in maintaining the balance between the peritoneal generation and degradation of fibrin by expressing the fibrinolytic enzyme tissue-type plasminogen activator (t-PA) as well as the specific plasminogen activator inhibitor-1 (PAI-1). In this study, we analyzed the effect of D-glucose and metabolically inert monosaccharides on the synthesis of t-PA and PAI-1 in cultured HMC.

Incubation of HMC with D-glucose or the metabolically inert monosaccharides mannitol and L-glucose (5-90 mM) resulted in a time- and concentration-dependent increase in t-PA mRNA expression and antigen secretion without affecting PAI-1 synthesis. A similar effect was evident when HMC were first exposed sequentially to pooled spent **peritoneal dialysis** effluent for up to 4 hours, and subsequently incubated for 20 hours in control medium. The stimulating effect of high D-glucose on t-PA expression in HMC was prevented by treating the cells with different **protein kinase C (PKC) inhibitors** (Ro 31-8220, Go 6976), but could not be mimicked by the PKC-activating phorbol eater PMA, indicating that this effect of high glucose is dependent on PKC activity, but not mediated through **PKC** activation. Also, using specific **inhibitors** (PD 98059, SE 203580) and activators (PMA, anisomycin, IL-1 alpha of the major routes of the mitogen-activated protein kinases (MAPKs) cascade, we found no evidence for a role of this cascade in regulating t-PA expression in HMC.

We conclude that hyperosmolarity induces t-PA (but not PAI-1) in HMC via a regulatory mechanism that requires active PKC, but that does not involve a major pathway in the MAPK cascade.

L85 ANSWER 13 OF 18 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 8
ACCESSION NUMBER: 1998:826012 SCISEARCH
THE GENUINE ARTICLE: 130YD
TITLE: High glucose increases prostaglandin E-2 synthesis in human peritoneal mesothelial cells: Role of hyperosmolarity
AUTHOR: Sitter T (Reprint); Haslinger B; Mandl S; Fricke H; Held E; Sellmayer A
CORPORATE SOURCE: UNIV MUNICH, KLINIKUM INNENSTADT, MED KLIN, ZIEMSSENSTR 1, D-80336 MUNICH, GERMANY (Reprint); UNIV MUNICH, KLINIKUM INNENSTADT, INST PROPHYLAXE KREISLAUFKRANKHEITEN, D-80336 MUNICH, GERMANY
COUNTRY OF AUTHOR: GERMANY
SOURCE: JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (NOV 1998) Vol. 9, No. 11, pp. 2005-2012.
Publisher: WILLIAMS & WILKINS, 351 WEST CAMDEN ST, BALTIMORE, MD 21201-2436.
ISSN: 1046-6673.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 39
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Peritoneal mesothelial cells are considered the pre-dominant source of peritoneal prostanoid formation because: they represent the largest resident cell population in the peritoneal cavity. The present study was designed to evaluate the effect of D-glucose, which is widely used in commercially available **peritoneal dialysis fluids** as an osmotic compound, on the synthesis of prostaglandins in cultured human mesothelial cells (HMC). Analysis of eicosanoid synthesis in HMC by reversed-phase HPLC revealed that 6-keto-PGF(1 alpha), the spontaneous hydrolysis product of prostacyclin (PGI(2)), and prostaglandin E-2 (PGE(2)) were the main eicosanoids produced. Addition of

D-glucose resulted in a time- and concentration-dependent (30 to 120 mM) increase in PGE(2) production in HMC (24 h, 90 mM: 3.9 +/- 0.5 ng/10(5) cells versus 2.3 +/- 0.3 in untreated cells; P < 0.05). Mannitol (90 mM) or L-glucose (90 mM), nonmetabolizable osmotic compounds, also led to a significant (P < 0.05) but less intense increase in PGE(2) synthesis (3.3 +/- 0.4 and 3.2 +/- 0.5 ng/10(5) cells, respectively). Increased PGE(2) synthesis was completely blunted by coincubation With the specific **protein kinase C (PKC) inhibitor** Ro 31-8220 or downregulation of PKC activity by preincubation with phorbol myristate acetate for 16 h. Furthermore, coincubation with PD 98059, an inhibitor of the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, also inhibited increased PGE(2) synthesis by D-glucose or mannitol. In contrast, the iso-osmolar glucose polymer icodextrin, which is used as an alternative to D-glucose in **peritoneal dialysis solutions**, had no effect on PGE(2) synthesis. These data indicate that D-glucose and metabolically inert sugars increase PGE(2) synthesis in NMC at least in part by hyperosmolarity and that this effect requires activation of PKC and the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway of intracellular signaling.

L85 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
ACCESSION NUMBER: 2000:645802 CAPLUS
DOCUMENT NUMBER: 133:217700
TITLE: **Inhibition of protein kinase C** to treat permeability failure in **peritoneal dialysis** for kidney failure
INVENTOR(S): King, George Liang
PATENT ASSIGNEE(S): Joslin Diabetes Center, Inc., USA
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000053013	A1	20000914	WO 2000-US6405	20000310

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-124043P P 19990312
AB The invention features a method of treating a subject having a permeability disjunction whereby an inhibitor of PKC (protein kinase C), e.g. PKC .beta., is added to the **peritoneal dialysis** fluid and administered to a subject having renal failure. The invention also features an improved **peritoneal dialysis** fluid and methods of making such **dialysis** fluid.
IT **141436-78-4, Protein kinase C**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors; protein kinase C inhibition** to treat permeability failure in **peritoneal dialysis** for kidney failure)
IT **169939-94-0, LY333531**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**protein kinase C inhibition** to treat permeability failure in **peritoneal dialysis** for kidney failure)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L85 ANSWER 15 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:524483 BIOSIS
DOCUMENT NUMBER: PREV200000524483
TITLE: D-glucose increases the synthesis of tissue-type plasminogen activator (t-PA) in human **peritoneal** mesothelial cells.
AUTHOR(S): Sitter, T. (1); Mandl-Weber, S.; Woernle, M.; Haslinger, B.; Goedde, M.; Kooistra, T.
CORPORATE SOURCE: (1) Klinikum Innenstadt, Ludwig-Maximilians-Universitaet, Munich Germany
SOURCE: Kidney & Blood Pressure Research, (1999) Vol. 22, No. 4-6, pp. 328-329. print.
Meeting Info.: Joint Scientific Meeting of the Society for Nephrology and the German Working Group for Clinical Nephrology Freiburg, Germany September 18-21, 1999
ISSN: 1420-4096.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L85 ANSWER 16 OF 18 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-549069 [61] WPIDS
CROSS REFERENCE: 2001-089951 [08]; 2002-255928 [30]
DOC. NO. CPI: C2001-163360
TITLE: New method for treating diabetic nephropathy or microalbuminuria in a diabetic individual comprises administration of a metabolite of a Salviae miltiorrhizae Radix herb.
DERWENT CLASS: B04
INVENTOR(S): JUNG, M; LEE, H C; LI, H; SHAH, S V
PATENT ASSIGNEE(S): (SHIV-N) SHIVA BIOMEDICAL LLC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6267992	B1	20010731	(200161)*		16

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6267992	B1	Cont of	US 1999-408436	19990929
			US 2000-666623	20000921

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 6267992	B1	Cont of	US 6149915

PRIORITY APPLN. INFO: US 1999-408436 19990929; US 2000-666623 20000921
AB US 6267992 B UPAB: 20020513
NOVELTY - A method for treatment of diabetic nephropathy or

microalbuminuria in a diabetic individual comprises administration of a metabolite of a salviae miltiorrhizae Radix herb (I) to the individual.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) methods for treating diabetic nephropathy or microalbuminuria comprising:

(i) determining the level of protein in urine of the diabetic individual;

(ii) comparing the level of protein in urine with a control level, and

(iii) administering (I) to lower the level of protein in urine of the diabetic to the control level or to restore the level of albumin in urine to the control level; and

(2) a method for treating microalbuminuria comprises:

(i) forming a metabolite to (I); and

(ii) administration of (I).

ACTIVITY - Antidiabetic; gynecological; antianginal; antiinflammatory.

No biological data given.

MECHANISM OF ACTION - **Protein kinase C inhibitor**; TGF- beta **inhibitor**, phosphorylated **inhibitor**, ERK inhibitor, MEK in mesangial cell inhibitor.

The salt of lithospermic acid (extract of (A)) (50 or 25 micro g/ml) (in vivo) decreased protein kinase C activity from 50 pmol/min to less than 40 or 20 pmol/min with addition of 50 or 25 micro g/ml lithospermic acid, respectively.

USE - For treating diabetic nephropathy or microalbuminuria in an diabetic individual (claimed), human conditions such as menstrual disorders, menostatis, menorrhagia, insomnia, blood circulation diseases, angina pectoris, inflammation and certain kidney diseases.

ADVANTAGE - The method is cost effective and without significant adverse side effects, especially in individuals who have had the condition for an extended time and where clinical management strategies are difficult to implement. The method provides an efficient way to treat and reduce the severity of kidney disease and ultimately, renal failure in diabetic patients; and can potentially halt, reverse or diminish the progression of diabetic nephropathy or microalbuminuria, thus increasing quality of life and life expectancy, without invasive medical interventions such as renal **dialysis** and kidney transplants. The herb lowers the level of protein or restore the level of albumin in the urine of the diabetic individual to about that of the control level.

Dwg.0/8

L85 ANSWER 17 OF 18 WPIDS (C) 2002 THOMSON DERWENT

ACCESSION NUMBER: 1999-571591 [48] WPIDS

DOC. NO. CPI: C1999-166761

TITLE: Treatment of renal dysfunction using selective beta-isozyme **protein kinase C inhibitors**, preferably **bis-indolyl-maleimide** compound.

DERWENT CLASS: B02

INVENTOR(S): GILBERT, R; WAYS, D K; GILBERT, R E

PATENT ASSIGNEE(S): (ELIL) LILLY & CO ELI; (GILB-I) GILBERT R E

COUNTRY COUNT: 86

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9944599	A1	19990910	(199948)*	EN	29

RW: EA GH GM KE LS MW OA SD SL SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

EP 951903 A1 19991027 (199950) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
AU 9929047 A 19990920 (200007)
ZA 9901784 A 20000223 (200016) 25
US 6225301 B1 20010501 (200126)
JP 2002505278 W 20020219 (200216) 42

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9944599	A1		WO 1999-US5447	19990305
EP 951903	A1		EP 1999-200660	19990305
AU 9929047	A		AU 1999-29047	19990305
ZA 9901784	A		ZA 1999-1784	19990305
US 6225301	B1	Provisional	US 1998-76852P	19980305
			US 1999-253718	19990222
JP 2002505278	W		WO 1999-US5447	19990305
			JP 2000-534201	19990305

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9929047	A	Based on	WO 9944599
JP 2002505278	W	Based on	WO 9944599

PRIORITY APPLN. INFO: US 1998-76852P 19980305; US 1999-253718 19990222

AB WO 9944599 A UPAB: 19991122
NOVELTY - A method for inhibiting intraglomerular hypertension, glomerulosclerosis or glomerular-intestitial fibrosis, or associated renal dysfunction, involves administration of a **protein kinase C** (**PKC**) beta - isozyme **inhibitor** (I).
ACTIVITY - Renal function improvement.
MECHANISM OF ACTION - **PKC** beta -isozyme **inhibitor** . (I) are especially selective beta -1 or beta -2 isozyme inhibitors. They are thought to reduce intraglomerular pressure and levels of transforming growth factor - beta .
USE - For treating renal dysfunction associated with abnormal glomerular activity, especially renal insufficiency or acute or chronic renal failure.
ADVANTAGE - Treatment with (I) provides a method of controlling certain renal disorders without recourse to renal **dialysis**.
Dwg.0/0

L85 ANSWER 18 OF 18 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1996-426812 [43] WPIDS
CROSS REFERENCE: 1996-426820 [43]
DOC. NO. CPI: C1996-134478
TITLE: Injectable nano-suspension of staurosporin deriv. with poor solubility - esp. N-benzoyl deriv., with polyoxyethylene-polyoxypropylene block copolymer and opt. phospholipid in water-ethanol, used to treat tumours.
DERWENT CLASS: A25 A96 B02 B07
INVENTOR(S): VAN HOOGEVEST, P; WEDER, H G; WEDER, H
PATENT ASSIGNEE(S): (CIBA) CIBA GEIGY AG; (VESI-N) VESIFACT AG; (NOVS) NOVARTIS AG; (NOVS) NOVARTIS-ERFINDUNGEN VERWALTUNGS GMBH; (NOVS) NOVARTIS CORP
COUNTRY COUNT: 26
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 733358	A2	19960925	(199643)*	GE	8
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
NO 9601136	A	19960923	(199647)		
NO 9601137	A	19960923	(199647)		
AU 9648094	A	19961003	(199650)		
AU 9648095	A	19961003	(199650)		
JP 08268893	A	19961015	(199651)		8
JP 08268915	A	19961015	(199651)		8
ZA 9602248	A	19961129	(199702)		19
ZA 9602249	A	19961129	(199702)		17
CA 2172110	A	19960922	(199704)		
CA 2172111	A	19960922	(199704)		
NZ 286207	A	19970424	(199723)		
NZ 286206	A	19970526	(199727)		
HU 9600700	A2	19970228	(199748)		
HU 9600701	A2	19970228	(199748)		
US 5726164	A	19980310	(199817)		8
MX 9601033	A1	19970901	(199850)		
MX 9601032	A1	19981101	(200022)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 733358	A2	EP 1996-810150	19960312
NO 9601136	A	NO 1996-1136	19960320
NO 9601137	A	NO 1996-1137	19960320
AU 9648094	A	AU 1996-48094	19960315
AU 9648095	A	AU 1996-48095	19960315
JP 08268893	A	JP 1996-63194	19960319
JP 08268915	A	JP 1996-63092	19960319
ZA 9602248	A	ZA 1996-2248	19960320
ZA 9602249	A	ZA 1996-2249	19960320
CA 2172110	A	CA 1996-2172110	19960319
CA 2172111	A	CA 1996-2172111	19960319
NZ 286207	A	NZ 1996-286207	19960319
NZ 286206	A	NZ 1996-286206	19960319
HU 9600700	A2	HU 1996-700	19960320
HU 9600701	A2	HU 1996-701	19960320
US 5726164	A	US 1996-619068	19960320
MX 9601033	A1	MX 1996-1033	19960319
MX 9601032	A1	MX 1996-1032	19960319

PRIORITY APPLN. INFO: CH 1995-804 19950321

AB EP 733358 A UPAB: 20000508

Pharmaceutical compsn. for intravenous admin. of staurosporin deriv. (A) with low solubility in water comprises (A); a polyoxyethylene-polyoxypropylene block copolymer (B); ethanol and water as transport materials; and opt. a phospholipid of formula (I) or its salts, and/or other adjuvants. R1 = 10-20C acyl, R2 = H or 10-20C acyl, R3 = H, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl, 1-4C alkyl, 1-5C alkyl substd. by carboxy, 2-5C hydroxyalkyl (opt. substd. by carboxy), 2-5C alkyl (substd. by carboxy and amino), inositol or glyceryl.

Also claimed is the prepn. of the compsn. by mixing all the components to form a homogenous dispersion; and (1) adding more water and opt. adjuvants, filtering, and opt. **dialysing** to give a clear soln.; or (2) filtering, opt. **dialysing**, drying the dispersion (opt. with addn. of adjuvants) and reconstitution of the dry prepn. to an injectable dispersion.

Also claimed is a nanosuspension contg. (A).

USE - The nanosuspension contg. N-benzoyl-staurosporin is used in tumour therapy (claimed). Staurosporin and its derivs. **inhibit protein kinase C** and other protein kinases and are used to restrict tumour growth, as antiinflammatory agents, as antibiotics, in the treatment of arteriosclerosis and diseases of the cardiovascular system and central nervous system.

ADVANTAGE - The nanosuspension is homogenous and stable, and can be prepared by a simple, conventional mixing process.
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